

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204781Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 204-781

SUPPL #

HFD # 160

Trade Name DOTAREM

Generic Name Gadoterate Meglumine

Applicant Name Guerbet

Approval Date, If Known March 20, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES x NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES x NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES x NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO x

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO x

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO x

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: James Moore
Title: Regulatory Health Project Manager
Date: March 7, 2013

Name of Office/Division Director signing form: Shaw Chen, M.D., Ph.D.
Title: Deputy Office Director, ODEIV

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES W MOORE
03/20/2013

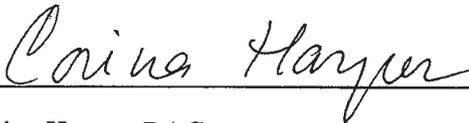
SHAW T CHEN
03/20/2013

Debarment Certification

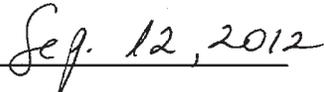
NDA 204-781 Dotarem® (gadoterate meglumine) Injection

In compliance with the Section 306(k) of Federal Food, Drug, and Cosmetic Act, 21U.S.C. §335a(k), as amended by the Generic Drug Enforcement Act of 1992, we Guerbet state the following with respect to this new drug application:

Guerbet hereby certifies that it knowingly did not and will not use in any capacity, the services of any person debarred under section 306, subsection (a) or (b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Corina Harper, RAC



Date

Head of North America Medical and Regulatory Affairs

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204-781	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: DOTAREM Established/Proper Name: gadoterate meglumine Dosage Form: Injection		Applicant: Guerbet Agent for Applicant (if applicable):
RPM: James Moore		Division: DMIP (HFD-160)
<p><u>NDAs and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: X 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>March 20, 2013</u> 		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		x None

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p>BLA: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<p><input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other</p>

Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)). 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

Copy of this Action Package Checklist ⁴	x
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	x Included
Documentation of consent/non-consent by officers/employees	x Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval March 20, 2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	x
• Original applicant-proposed labeling	x
• Example of class labeling, if applicable	

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	x
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	x-March 7, 2013 x-March 6, 2013
Labeling reviews (<i>indicate dates of reviews and meetings</i>)	x RPM March 20, 2013 x DMEPA March 14, 2013 <input type="checkbox"/> DMPP/PLT (DRISK) x ODPD (DDMAC) February 20, 2013 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	X March 21, 2013
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	x Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes x No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>March 6, 2013</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	x Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	x Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	x
❖ Internal memoranda, telecons, etc.	None
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	x No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	x June 12, 2012
• EOP2 meeting (<i>indicate date of mtg</i>)	none
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	
❖ Advisory Committee Meeting(s)	x
• Date(s) of Meeting(s)	February 14, 2013
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	x
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	x None March , 2013
Division Director Summary Review (<i>indicate date for each review</i>)	x March 8, 2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	x None February 26, 2013
PMR/PMC Development Templates (<i>indicate total number</i>)	x None
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	X February 10, 2013
• Clinical review(s) (<i>indicate date for each review</i>)	X February 9, 2013
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	x
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	X (See Clinical Review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	x None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	x Not applicable
❖ Risk Management	
• REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	x None

⁶ Filing reviews should be filed with the discipline reviews.

OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)	x
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	x February 26, 2013
Statistical Team Leader Review(s) (indicate date for each review)	x February 26, 2013
Statistical Review(s) (indicate date for each review)	x March 5, 2013
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	x February 20, 2013
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	x February 20, 2013
Clinical Pharmacology review(s) (indicate date for each review)	x February 20, 2013
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	x None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	x March 15, 2013
• Supervisory Review(s) (indicate date for each review)	x February 21, 2013, March 5, 2013
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	x February 21, 2013, March 5, 2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	x None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	x No carc
❖ ECAC/CAC report/memo of meeting	x None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	x None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	x March 7, 2013
• Branch Chief/Team Leader Review(s) (indicate date for each review)	x February 20, 2013
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	x February 20, 2013
❖ Microbiology Reviews x NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review)	X-February 11, 2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	x-February 21, 2013

Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>) (<i>all original applications and all efficacy supplements that could increase the patient population</i>)	X (See Chemistry Review)
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	X (See Chemistry Review)
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	X (See Chemistry Review)
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>)	Date completed: February 26, 2013 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

pendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's DRA.



NDA 204781

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Guerbet, LLC
1185 West 2nd Street
Bloomington, Indiana 47403

ATTENTION: Corina Harper, RAC
Head of North America Medical and Regulatory Affairs

Dear Ms. Harper:

Please refer to your New Drug Application (NDA) submitted and received September 20, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Gadoterate Meglumine, 0.2 ml/kg.

We also refer to your correspondence, dated and received December 7, 2012, requesting review of your proposed proprietary name, Dotarem. We have completed our review of the proposed proprietary name, Dotarem and have concluded that it is acceptable.

The proposed proprietary name, Dotarem, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

Additionally, if **any** of the proposed product characteristics as stated in you December 7, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Rimmel, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, James Moore at (301) 796-1986.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
03/07/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: March 13, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Information Re: Tcon, March 14, 2013, NDA 204-781, Dotarem Injection, Package Insert/PMRs	

Total no. of pages including cover: 2

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March 13, 2013

Regarding the telephone conference scheduled for tomorrow, March 14, 2013, at 12PM for Dotarem, NDA 204-781, the Division has the following response to your question about the points for discussion at the meeting.

FDA plans to discuss all the changes Guerbet made to the proposed Dotarem label, with a special focus upon the [REDACTED] ^{(b) (4)}

[REDACTED] FDA has concerns about almost all the proposed changes in the label and hopes to review these item by item. FDA also hopes to briefly discuss the proposed post-marketing requirements in pediatric patients aged less than two years.

If you have additional questions, please don't hesitate to contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
03/13/2013



Food and Drug Administration
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FACSIMILE TRANSMITTAL SHEET

DATE: March 12, 2013

To: Corina Harper, RAC, Compliance Manager	James Moore
Company: Guerbet	From: Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986

Subject: FDA Response to Guerbet Re:Chemistry Request 4, NDA 204-781, Dotarem, Expiry

Total no. of pages including cover: 3

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March 12, 2013

3/12/13 DENIAL OF REQUESTED EXPIRY/REQUEST FOR REVISION

Regarding your pending NDA for Dotarem, NDA 204-781, Guerbet's response dated March 11, 2013 to FDA's Chemistry Information Request 4 (CMC-IR-4) dated March 7, 2013, FDA has the following response.

We acknowledge the data referenced in your email correspondence of March 11, 2013, and the fact that you have provided stability data for different presentations to the NDA in the December 31, 2012 and the February 1, 2013 submissions. Based on these data the expiry period assignments were made to you as follows:

Based on the available stability data of 12 months CRT + 6 months accelerated, the expiration date for the product (vial and PFS) made with DOTA- (b) (4) is 18 months.

Based on the available stability data of 24 months CRT + 6 months accelerated, the expiration date for the product (vial) made with DOTA- (b) (4) is 30 months.

Based on the available stability data of 36 months CRT + 6 months accelerated, the expiration date for the product (PFS) made with DOTA- (b) (4) is 36 months.

We also acknowledge your statement on the similarities of the manufacturing processes between different sources of DOTA and expected sameness in their specifications. However for the stability expiry, the drug product manufactured in the intended final presentation, including the (b) (4) and the container-closure system, does not have full term data to support the requested (b) (4) Full term stability data for all presentations (b) (4) is expected at the time of the NDA submission in support of a proposed expiration period of (b) (4) (b) (4) Other stability tested periods may be filed at the time of submission, if previously agreed with FDA, but this does not guarantee approval of unsupported expiry period requests.

Therefore, your request for a (b) (4) expiry period, for all DOTAREM presentations, is not acceptable. We encourage you to supply an amendment to your NDA within the next 48 hours to propose the expiry time periods as we have outlined them. If you disagree with our proposal, please promptly confirm your position. We will not review new data within this review cycle.

Please provide your response to me electronically by COB, Thursday March 14, 2013 (within the next 48 hours), at James.Moore@fda.hhs.gov. Follow up your electronic response with a submission to your pending NDA application.

If you have questions, you may contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager

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/s/

JAMES W MOORE
03/13/2013



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: March 1, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Draft Labeling, NDA 204-781, Dotarem Injection	

Total no. of pages including cover: 2

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March 1, 2013

Regarding the draft labeling for your pending NDA 204-781 for Dotarem, you should revise your labeling as requested and provide the following.

Immediate Container Labels and Immediate Container Cartons - single dose presentation

1. Revise the composition statement on the label for the immediate container for the vials, the cartons for the vials, the prefilled syringes and the prefilled syringe cartons for all fill sizes to match the composition statement in the revised package insert as follows:

Each 1 mL contains: 376.9 mg of gadoterate meglumine, 0.25 mg DOTA and water for injection

PHARMACY BULK PACKAGE -PBP

2. The Immediate Container label for the 100 mL PBP vial and carton should state: **"NOT FOR DIRECT INFUSION"**
3. Revise the composition statement for the immediate container for the vials of the Pharmacy Bulk Package, and the cartons for the vials to match the composition statement in the revised package insert as follows:

Each 1 mL contains: 376.9 mg of gadoterate meglumine, 0.25 mg DOTA and water for injection

4. Provide a separate revised package insert for the single dose presentations and the pharmacy bulk package of Dotarem.

A draft of the revised package insert for the single dose presentations of your product is attached.

Send your response to me electronically at James.Moore@fda.hhs.gov. Provide your response by COB Wednesday, March 6, 2013. Follow up your electronic response with a submission to your NDA file.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JAMES W MOORE
03/05/2013



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Center for Drug Evaluation and Research
Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Pharmacology Request 2, NDA 204-781, Dotarem Injection, Product Excretion	

Total no. of pages including cover: 2

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January 30, 2013

Regarding your pending NDA for Dotarem NDA 204-781, the clinical pharmacology team has the following comments and information requests.

We are aware of the submitted data suggesting that DOTA, Ca-DOTA and cyclene are not excreted in animals.

While the human renal impairment study (Study DGD-3-28 A) contains a reference to human HPTLC results (page 27 of 270), from our review of the analytical methods used for the submitted human studies, it appears that all studies measured only total Gd.

1. Are the HPTLC results available, or have there been other attempts to determine if ^{(b) (4)} and/or ^{(b) (4)} are present in humans? If yes, please describe the method(s) and show the results to support that it is exclusively intact Gd-DOTA that circulates and is excreted. If no, is there data or reasoning beyond that included in Study DGD-3-28 A that underlies your assertion that it is exclusively intact Gd-DOTA that circulates and is excreted in humans?

Provide your response to me electronically at James.Moore@fda.hhs.gov. Also send a copy to Dr. Christy John at Christy.John@fda.hhs.gov and to Dr. Gene Williams at Gene.Williams@fda.hhs.gov. You should provide your response to FDA by COB Wednesday, February 6, 2013. Follow up your electronic submission with a submission to your pending NDA file.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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JAMES W MOORE
01/30/2013



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FACSIMILE TRANSMITTAL SHEET

DATE: January 11, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 16, NDA 204-781, Dotarem Injection, AE Severity Table	

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January 11, 2013

Regarding your pending NDA 204-781 for Dotarem, the clinical reviewer has the following information request.

1. Complete the table below.

N = 2813

Category	All AEs	Related AEs
No. of AEs		
No. (%) of Subjects with at least 1 AE		
Mild		
Moderate		
Severe		
Not reported/not collected		
No. (%) of subjects with at least 1 SAE		
No. (%) of deaths		
No (%) of subjects discontinued due to an AE		

Summary of Adverse Events by Subject Age in the Pediatric Population Study -050

Category	All AEs	Related AEs
No. of AEs		
No. (%) of Subjects with at least 1 AE		
2-6 years		
6-12 years		
12-18		
Most frequent AEs (No. and % by SOC and PT-all ages		

Send your response to me electronically as soon as possible at James.Moore@fda.hhs.gov and provide Dr. Barbara Stinson a copy at Barbara.Stinson@fda.hhs.gov. Follow up your response with a submission to your NDA.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
01/31/2013



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FACSIMILE TRANSMITTAL SHEET

DATE: January 10, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 15, NDA 204-781, Dotarem Injection, AE Table, Dose	

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January 10, 2013

Regarding your pending NDA 204-781 for Dotarem, the clinical reviewer has the following information request.

1. Please complete the table below.

Type of Study	Number of Patients Exposed to Dotarem	Patients With at Least one Adverse Event (AE) N (%)	Number of Serious Adverse Events (SAE)N (%)
PK			
CNS (Adults)			
Whole Body			
MRA			
CNS (Pediatric)			
Total	2813		

Send your response to me electronically by COB today, January 10, 2013 at James.Moore@fda.hhs.gov and provide Dr. Barbara Stinson a copy at Barbara.Stinson@fda.hhs.gov. Follow up your response with a submission to your NDA.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
01/31/2013



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FACSIMILE TRANSMITTAL SHEET

DATE: January 10, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 14, NDA 204-781, Dotarem Injection, AEs, Body System	

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January 10, 2013

Regarding your pending NDA 204-781 for Dotarem, the clinical reviewer has the following comments and information request.

1. Please provide a listing by number and percent for all AEs (number and percent to be a sum of related and non related) in the clinical trial population, in the CNS population, in the population for the two pivotal trials, and in the pediatric trials. For example, on page 15 of module 2.7.4 you state there are 363 AEs in 263 patients, related or not. The table that follows (table 9 on page 16) states that this is only for related AEs. What is the number and incidence for all AEs by SOC and by PT for the 49 trials, the CNS trials, the pivotal trials, and the pediatric trials (by age group)?

Send your response to me electronically by COB today, January 10, 2013 at James.Moore@fda.hhs.gov and provide Dr. Barbara Stinson a copy at Barbara.Stinson@fda.hhs.gov. Follow up your response with a submission to your NDA.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
01/31/2013



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: January 10, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 13, NDA 204-781, Dotarem Injection, safety data	

Total no. of pages including cover: 2

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January 10, 2013

Regarding your Pending NDA 204-781 for Dotarem, the clinical reviewer has the following information request and comment. In the Division Response to question 6 from the Pre-NDA meeting package the Division noted that while it was acceptable to submit safety data for Dotarem with a datalock date of 3-31-12, you were advised that you should provide safety data for the time period 3 months prior to submission of your NDA. To date that data has not been received. Note the Division's Preliminary Response below to question 6 from the Pre-NDA meeting package.

FDA's Response to Question 6:

This approach is acceptable. However since your anticipated date of submission is in September, the safety data for the submission should be extended to cover the time frame up to about 3 months prior to the submission. In addition, please be advised that a 120 day safety update will be required once the review is ongoing.

1. Provide safety data up to three months prior to your NDA submission.
2. Also, you should provide a Safety Update to your NDA.

Send your response to item 1 to me electronically as soon as possible at James.Moore@fda.hhs.gov and provide Dr. Barbara Stinson a copy at Barbara.Stinson@fda.hhs.gov. Send your Safety Update to the same addressees by COB Tuesday, January 22, 2013. Follow up your response with a submission to your NDA.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
01/31/2013



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 12, NDA 204-781, Dotarem Injection, Subjects, AEs	

Total no. of pages including cover: 2

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January 8, 2013

Regarding your pending NDA for Dotarem, the clinical reviewer has the following comments and information requests.

1. At the pre NDA meeting you noted a total of 2866 subjects exposed to Dotarem. For the NDA, the safety database is based on 2813 exposures. Please account for the differences in number.
2. Also at the Pre-NDA meeting you cited that 25 SAEs were associated with the 2866 subjects, but in the NDA you cite 23 AEs associated with 2813 subjects. Please account for the differences in number.
3. Please provide the number of pediatric subjects treated per age group up to age 17 years (through age 16).
4. Please provide a similar listing for subjects in the -050 study, by age group (2 through 16 years).

You should provide your response to me electronically at James.Moore@fda.hhs.gov and provide a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov. Follow up your electronic response to me with a submission to your NDA. You should respond to this request by COB, Today, January 8, 2013.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
01/31/2013



Food and Drug Administration
 Center for Drug Evaluation and Research
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FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 11, NDA 204-781, Dotarem Injection, Diagnostic Information	

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January 8, 2013

Regarding your pending NDA 204-781 for Dotarem, the clinical team has the following comments and information requests.

Regarding the Study Report number DGD-44-050:

We are trying to obtain a better understanding of the primary endpoint analyses and the patient population. We are particularly concerned that the “patient score” approach that is used in the primary endpoint may not be the most clinically appropriate format for displaying the primary endpoint results (even though the analyses may achieve their regulatory & study goals). Typically patient level information is important when an imaging test is used to make a diagnosis for a patient (such as detecting cancer or the presence of amyloid). However, for a contrast agent with a goal of improving detection/characterization of lesions on an image, a lesion-level display of the data may be most clinically relevant since the main focus is upon improving lesion visibility on the images.

- 1) We are trying to understand the difference between the FAS and the PP population definitions. If we understand correctly, the FAS population (which is the primary endpoint analytical population) consists of all patients who had “valid” assessments of the 3 co-primary endpoints (excerpt from study report). The SAP defines the FAS as the population of patients with “available” assessments of the three co-primary endpoints. Hence, the definitions of the FAS population appear to differ between the study report and the SAP (“valid” versus “available”).
 - a. The SAP provides more detail on the FAS analytical methods such that it appears the FAS population actually consists of all patients who have any lesion on either the “pre” or the “paired” images—is this correct? If so, was this done in your analyses of the FAS population? The “example” in the SAP appears to indicate that all patients in the FAS population have at least one lesion on either the “pre” or the “paired” images. Please clarify.
 - b. We understand the PP population definition is confined to patients who have at least one lesion on the “paired” images—is this correct? If not, please clarify.
- 2) The definitions of FAS and PP population may play some role in the observation that, in Table 11.5-5, the sample size (N patients) shows that more patients had images interpreted in the “paired” reads than in the “pre” reads. This imbalance might bias the study results in favor of your drug since the “patient score” appears to be inflated if more patients are counted in the “paired” read than in the “pre” read. The difference in the number of patients with interpreted images does not appear clinically logical since all patients were required to have “pre” images (as verified by Table 11.5-3, where the sample sizes are the same for “pre” and

“paired”). Too, the FAS approach was supposed to involve imputation for missing data (such that the “pre” and “paired” patient sample sizes should be the same). Given these considerations, please explain why the “pre” and “paired” patient sample sizes differ in Table 11.5-5 (most other tables share this imbalance in patient sample sizes).

- 3) We cannot identify the role that the “concordance reading” played in the endpoint analyses. The SAP states that, “A matching lesions process (concordance reading), involving a fourth independent reader, will be carried out to ensure the concordance of lesions between different MRI modalities and between the readers.” What endpoint was impacted by the “concordance reading”? Were any analyses performed to assess agreement among readers for the (3 point scale/co-primary endpoint) scoring of specific lesions? We understand that Table 11.5-21 and Table 11.5-22 simply shows “agreement” among readers for “patient scores,” not the reader agreement upon the scoring of individual lesions—correct? Why are the inter-reader “agreement” results for “patient scores” so poor?

Regarding Study 050 and 051:

- 4) To try to better display the two phase 3 study results in a clinically-interpretable manner, please develop a table that approximates the following example.

“In studies A and B, lesions were scored on a scale of 0 (unevaluable), 1 (seen incompletely) to 2 (“completely seen”). Tables 1 through 3 shows the number and proportion of lesions scored as 2, 1 and 0 among the total number of lesions detected on pre-contrast and paired (pre-contrast + contrast) images in these studies.

Table 1. Proportion (%) of “Completely Seen” Lesions in Studies A and B by Reader*

Outcome	Study A			Study B		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
<i>Border Delineation</i>						
Pre	n/n2 (X%)					
Paired						
<i>Internal Morphology</i>						
Pre						
Paired						
<i>Contrast Enhancement</i>						
Pre						
Paired						

*each reader’s cell shows the number of lesions scoring 2 (the numerator) divided by the total number of lesions detected by the reader (the denominator)”

Table 2. Proportion (%) of “Incompletely Seen” Lesions in Studies A and B by Reader*

Outcome	Study A			Study B		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
<i>Border Delineation</i>						
Pre	n/n2 (X%)					
Paired						
<i>Internal Morphology</i>						
Pre						
Paired						
<i>Contrast Enhancement</i>						
Pre						
Paired						

*each reader’s cell shows the number of lesions scoring 1 (the numerator) divided by the total number of lesions detected by the reader (the denominator)”

Table 3. Proportion (%) of “Unevaluable” Lesions in Studies A and B by Reader*

Outcome	Study A			Study B		
	Reader 1	Reader 2	Reader 3	Reader 1	Reader 2	Reader 3
<i>Border Delineation</i>						
Pre	n/n2 (X%)					
Paired						
<i>Internal Morphology</i>						
Pre						
Paired						
<i>Contrast Enhancement</i>						
Pre						
Paired						

*each reader’s cell shows the number of lesions scoring 0 (the numerator) divided by the total number of lesions detected by the reader (the denominator)”

Regarding Study 051:

The report for Study DGD-3-44 describes the primary endpoint as “diagnostic accuracy” when images are compared to a histology truth standard. The cited original protocol for this study does not mention a histology truth standard; instead, the protocol says “diagnostic contribution” was the primary endpoint. Apparently there were many amendments to the original DGD-3-44 protocol (which we cannot locate in your NDA submission). Supply the basis for the DGD-3-44 study report citing a primary endpoint of “diagnostic accuracy.” Was this derived from the protocol amendments? (if so, please supply a copy of those amendments).

You should provide your response to me electronically at James.Moore@fda.hhs.gov. Follow up your electronic response to me with a submission to your NDA. You should respond to this request by COB Friday, January 11, 2013.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
01/31/2013



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FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 10, NDA 204-781, Dotarem Injection, Dosing	

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January 8, 2013

Regarding your pending NDA 204-781 for Dotarem the clinical reviewer has the following information request.

For the phase 4 study DGD-3-29, please provide as an individual subject listing for all 50 subjects the original study report data referable to drug injection (volume administered, manner of injection, etc.) in the same manner of presentation as for studies DGD-3-15 and DGD-3-16.

You should provide your response to me electronically at James.Moore@fda.hhs.gov and provide a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov. Follow up your electronic response to me with a submission to your NDA. You should respond to this request by COB, Today, January 8, 2013.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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JAMES W MOORE
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FACSIMILE TRANSMITTAL SHEET

DATE: January 8, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Statistical Request 1, NDA 204-781, Dotarem Injection, datasets	

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January 8, 2013

Regarding your pending NDA 207-481 for Dotarem, the statistical reviewer has the following comments and information requests.

As discussed in the telecon today (Jan 8, 2012 11:45 AM EST), please provide the information for the following variables to be added to the current datasets named READERS for two studies (DGD-44-050 & DGD-44-051) and datasets in the xpt format for the pediatric population:

Country Code

Geographic Region

Treatment (Dotarem, Magnevist)

Age

Gender

Weight

Race

Actual dose given (millimole per kilogram)

FAS (1=Yes, 0=No)

PP (1=Yes, 0=No)

Number of lesions seen in a patient (1 to 5)

Size of each Lesion (1=small, 2=medium, 3=large) – lesion1, lesion2, to lesion 5

Sum of all lesion scores

Primary Variable (Paired – Pre)

Also (Post – Pre)

Data for pediatric population

Provide the revised datasets (READERS) for the two studies and for the pediatric population along with the revised definition file to me electronically at James.Moore@fda.hhs.gov. Provide a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov and to Dr. Satish Misra at Satish.Misra@fda.hhs.gov. Follow up your electronic response to me with a submission to your NDA. You should respond to this request by 12PM, Wednesday, January 9, 2013.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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JAMES W MOORE
01/12/2013



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FACSIMILE TRANSMITTAL SHEET

DATE: January 7, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 9, NDA 204-781, Dotarem Injection, Labs	

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January 7, 2013

Regarding your pending NDA for Dotarem, NDA 204-781, the clinical reviewer has the following information request.

1. Please provide the number of subjects in the dgd-3-15 trial that were monitored by laboratory parameters. The study report indicates that 29 were enrolled but states that labs were obtained for only 20.

You should provide your response to me electronically at James.Moore@fda.hhs.gov and provide a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov. Follow up your electronic response to me with a submission to your NDA. You should respond to this request by COB, Tuesday, January 7, 2013.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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JAMES W MOORE
01/31/2013



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FACSIMILE TRANSMITTAL SHEET

DATE: January 4, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 8, NDA 204-781, Dotarem Injection, Dosing, Demographics	

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January 4, 2013

Regarding your pending NDA 204-781 for Dotarem, the clinical reviewer has the following information requests.

1. Please provide an **actual** dose range (minimum, maximum, and mean) for **all** 2813 subjects in Dotarem clinical trials, reported as **mmol/kg BW**. Please provide a similar listing for each of the 23 CNS trials.
2. Please note how many subjects, **total number and number in CNS trials**, received the theoretical dose of 0.1, 0.2, or 0.3 mmol/kg \pm 10%. For example, for 0.1 mmol/kg the dose range is 0.09-0.11 mmol/kg. If a subject received more than one dose of Dotarem, report using the cumulative dose.
3. For item number 2 above please subdivide the listing to adults, pediatric subjects between 2 years and 18 years, and subjects under age 2 years.
4. For all clinical trials, please stratify AE number and rate by dose as follows: < 0.05 mmol/kg, 0.05-< 0.09 mmol/kg, 0.09-<0.11 mmol/kg, 0.11-<0.2 mmol/kg, 0.2-<3 mmol/kg, and 3 mmol/kg or greater.
5. Using the dose ranges above, please provide a breakdown of the age range, mean age, and racial group studied for each dose.
6. For older pediatric subjects, please clarify the age of the pediatric population that was studied for which the upper limit is listed as both 17 and 18 years.
7. For item number 5 above please include gender in the dose breakdown.
8. Regarding dose stratification for number 5 above, please include by dose administered (mmol/kg) the AEs by number and per cent in subjects with renal impairment (by elevated creatinine or eGFR < 60 mL/min), subjects with hepatic impairment (by ALT and AST), subjects with and without cardiovascular disease, subjects with allergies, and subjects with contrast allergies. Please report as all AEs and as drug related AEs.

You should provide your response to me electronically at James.Moore@fda.hhs.gov and provide a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov. Follow up your electronic response to me with a submission to your NDA. You should respond to this request by Noon, Monday, January 7, 2013.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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JAMES W MOORE
01/31/2013



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FACSIMILE TRANSMITTAL SHEET

DATE: January 3, 2013

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986

Subject: Clinical Request 7, NDA 204-781, Dotarem Injection, Dosing

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January 3, 2013

For your pending NDA 204-781 (Dotarem), the clinical reviewer has the following information requests.

1. Please provide an **actual** dose range (minimum, maximum, and mean) for **all** 2813 subjects in Dotarem clinical trials, reported as **mmol/kg BW**. Please provide a similar listing for each of the 23 CNS trials.
2. Please note how many subjects, **total number and number in CNS trials**, received the theoretical dose of 0.1, 0.2, or 0.3 mmol/kg \pm 10%. For example, for 0.1 mmol/kg the dose range is 0.09-0.11 mmol/kg. If a subject received more than one dose of Dotarem, report using the cumulative dose.
3. For item number 2 above, please subdivide the listing to adults, pediatric subjects between 2 years and 18 years, and subjects under age 2 years.
4. For all clinical trials, please stratify AE number and rate by dose as follows: < 0.05 mmol/kg, 0.05-< 0.09 mmol/kg, 0.09-<0.11 mmol/kg, 0.11-<0.2 mmol/kg, 0.2-<3 mmol/kg, and 3 mmol/kg or greater.
5. Using the dose ranges above, please provide a breakdown of the age range, mean age, and racial group studied for each dose.
6. For older pediatric subjects, please clarify the age of the pediatric population that was studied for which the upper limit is listed as both 17 and 18 years.

You should provide your response to me electronically at James.Moore@fda.hhs.gov and provide a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov. Follow up your electronic response to me with a submission to your NDA. You should respond to this request by Noon, Friday, January 4, 2013.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
01/28/2013



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FACSIMILE TRANSMITTAL SHEET

DATE: December 14, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 6, NDA 204-781, Dotarem Injection, Safety	

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December 14, 2012

Regarding your pending NDA for Dotarem NDA 204-781, the clinical reviewer has the following comments and information requests.

1. For the -051 study (DGD-3-44), please provide the vital signs values which were pre-specified by you as abnormal and clarify what changes in the vital signs were defined as abnormal, for example change in number of heart beats or change in blood pressure parameters.
2. Please provide the number and percent of subjects in the -051 study who have undergone vital sign evaluation, Adverse Event (AE) evaluation, and both, at all five pre specified time points (pre injection, 5 minutes, 15 minutes, 1 hour, and 2 hours).
3. Please provide the number and percent of subjects in the -051 study who, in addition to all of the above five time points. have also presented for 24 hour follow up. Note the same for the 48 and 72 hour follow up (i.e. all subjects to have 6, 7, or 8 safety points). Note how many of these subjects received vital sign and AE evaluation and how many received only AE evaluation.
4. Please provide the number and percent of subjects in the -051 study who presented for the 24 hour follow up, regardless of whether the subject was followed up at all of the previous time points. Please provide the same information for the 48 hour and 72 hour follow up intervals. Note how many of these subjects received vital sign and AE evaluation and how many received only AE evaluation.
5. For the -050 study, please note the pre-specified abnormal values for the various vital signs and laboratory parameters that were monitored.
6. For the -050 study, please note the number and percent of subjects who presented for follow up at all study time point intervals (baseline, 5 minutes, 15 minutes, and 24 hours for vital signs and baseline, and 24 hours for laboratory parameters). In addition to noting this as a percent of the total population enrolled, please divide this into pediatric subjects, adults who received Dotarem, and adults who received Magnevist.
7. Please provide normal laboratory values for the studies where the clinical range is reported as missing, for example DGD-44-049.

You should provide your response to me electronically at James.Moore@fda.hhs.gov and provide a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov. Follow up your electronic response to me with a submission to your NDA. You should respond to this request by COB Tuesday, December 18, 2012.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
12/19/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: December 13, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 5, NDA 204-781, Dotarem Injection, Clinical Sites	

Total no. of pages including cover: 2

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Document to be mailed: YES x NO

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December 13, 2012

Regarding your pending NDA for Dotarem (NDA 204-781), the clinical reviewer has the following information request.

1. In countries where your clinical sites were located, what percent of the subjects were from Europe, the United States, Latin America, and South Korea?
2. For Europe and Latin America which countries contributed the largest percentage of subjects to the trials?

Send your response to me electronically at James.Moore@fda.hhs.gov and provide a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov. Provide this document electronically to me by COB Monday, December 17, 2012. Follow up your electronic response to me with a submission to your NDA file.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
12/14/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: December 13, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Chemistry Request 3, NDA 204-781, Dotarem, Stability, Description	

Total no. of pages including cover: 3

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December 13, 2012

**Product Quality
Additional Information Request**

Regarding your pending NDA 204-781 for Dotarem, the reviewing chemist has the following comments and information requests.

1. Provide representative certificates of analysis for DOTA, final intermediate prepared and controlled by each manufacturer, (b) (4).
2. Provide a master batch record for the commercial size batch of DOTA as performed at each manufacturing site ((b) (4)
3. Assign an expiry time and storage conditions for the DOTA final intermediate based on available stability data.
4. Provide the following information on the DOTA reference standard:
 - a) Specifications on the test methods and acceptance limits for its quality.
 - b) Synthetic scheme if this is different from the one used to prepare the DOTA final intermediate component.
5. Establish a retesting period for (b) (4) based on stability data or the manufacturer's information and recommendations.
6. Provide the source(s) and a representative certificate of analysis of the (b) (4) reference standard material used during the assay and (b) (4) impurity testing of (b) (4)
7. Provide an accurate representation of the structural formula of gadoterate meglumine, as you have explained in section 3.2.S.3.1. It is described as an octadentated gadolinium complex involving the coordination of Gd with 4 nitrogen and 4 oxygen atoms and a ninth coordination site for a water molecule appears to be justified by literature data. The structural formula of gadoterate meglumine should illustrate all binding sites clearly and accurately and it should be consistently used throughout the application. Specifically, revise module 2 and 3 sections 3.2.S.1.2, 3.2.P.2 as well as, in the package insert - description section.
8. The final drug product, DOTAREM Injection should be tested for decomposition products estimated against DOTA gadoteric acid and meglumine as is customary for other gadolinium products in the USA market. The impurity profile should be part of the release and stability testing of this final product.
9. Provide primary stability data for both vials and syringes to support the proposed (b) (4) expiration time.

10. Provide the methodology and calculations used by Guerbet for the determination of the thermodynamic and conditional stability constants for the GdDOTA complex referenced in your cited literature Port et al. (2008), Table 1 and Moreau et al. (2004).

Send your response to me electronically at James.Moore@fda.hhs.gov and send a copy to Dr. Milagros Salazar Driver at Milagros.Salazar@fda.hhs.gov. Provide this information by as soon as possible but not later than COB December 31, 2012. Follow up this response with a submission to your IND file.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
12/13/2012



NDA 204-781

FILING COMMUNICATION

Guerbet LLC
Attention: Corina Harper, RAC
Head of North America Scientific Office
1185 West 2nd Street
Bloomington, IN 47403

Dear Ms. Harper:

Please refer to your New Drug Application (NDA) dated September 20, 2012, received September 20, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Dotarem[®] (gadoterate meglumine) Injection 376.9mg/mL.

We also refer to your amendments dated October 30, November 6 and 16, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is March 20, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 27, 2013. An Advisory Committee Meeting is tentatively scheduled for February 14, 2013.

During our filing review of your application, we identified the following potential review issues:

1. You only submitted the package insert for the pharmacy bulk package product presentation. The package insert for the vial and syringe presentations are absent from your submission.

2. In the submitted package insert, you state that the recommended dose of Dotarem is “1-2 mL/second for [REDACTED] (b) (4) However, there appears to be a lack of consistent data to support such a statement.

In the three pediatric studies you submitted to support the pediatric indication for your product, different rates of administration appear to have been used, none being fully consistent with what you are proposing in the labeling.

In addition, the provided publications cited for support of the pediatric use of your product all appear to employ different doses.

This is problematic, especially in view of the fact that we are unable to find in your application any dose ranging studies, in general, or any pediatric pharmacokinetics studies, in particular.

3. We are concerned about the risk associated with the use of gadolinium based contrast agents in children less than two years of age. We note that, in the three pediatric studies you submitted to support the pediatric indication for your product, there were only seven patients less than two years of age. Therefore, your application appears to lack sufficient clinical data to justify the indication, especially from the risk perspective, for use of your product in this patient population.

We understand that sources of data other than those originating in adequate and well controlled clinical trials could be supportive of an indication and plan to further vet the issue of the pediatric indication during a meeting of an advisory committee.

4. We also note that the application lacks animal data which could help support the safe use of your product in patients less than two years of age.
5. The overall safety database submitted with your application might prove to be insufficient as only some of the patients appear to have had adequate monitoring of laboratory parameters following Dotarem administration.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the package insert for the syringe and vial presentations of your product.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have submitted pediatric studies with this application, and you have not requested a partial waiver or deferral for any additional studies. Once the review of this application is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call James Moore, Regulatory Health Project Manager, at (301) 796-1986.

Sincerely,

{See appended electronic signature page}

Rafel D. Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

JAMES W MOORE
12/03/2012

RAFEL D RIEVES
12/03/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: November 7, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Pharmacology Request 1, NDA 204-781, Dotarem Injection, ECG	

Total no. of pages including cover: 2

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November 7, 2012

The team reviewing your electrocardiographic study for Dotarem NDA 204-781 has the followings requests.

1. Please complete the table below.

Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat,

		standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

2. Please submit all related ECG waveforms to the ECG warehouse at www.ecgwarehouse.com.

Please complete the table, and submit the additional information as requested. Send a copy to me at James.Moore@fda.hhs.gov and a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov . You should submit this information as soon as possible. Follow up your electronic response to me with a submission to your pending NDA file.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
11/07/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: November 7, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Pharmacology Request 1, NDA 204-781, Dotarem Injection, Language Translation	

Total no. of pages including cover: 2

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November 7, 2012

Regarding your pending NDA for Dotarem NDA 204-781, the pharmacology reviewer has the following comments and information requests.

Please provide the English translation of portions of the nonclinical study reports as listed in the Table below. In addition, please ensure that all nonclinical sections of the NDA are rendered in the English language.

NDA 204-781 - List of Studies containing Section(s) in French

No.	Study	Study Number	Page Number(s)	CTD Location
1	Safety pharmacology study in dogs	DGD-2-4-A	4 of 38	4.2.1.3.1
2	Rat acute Toxicity	99-12-810	25-35 of 48	
3	Rat single dose Toxicity	99-12-807	117-118; 120-129 of 241	
4	DRF study in dog single dose Toxicity	99-12-811	26-43 of 76	4.2.3.1.1
5	Dog single dose Toxicity	99-12-808	173-175; 178-186 of 273	
6	Rat 4-week Toxicity	99-12-806	141-164 of 270	4.2.3.2.1
7	Rat 7-day Toxicity	99-12-805	37-45 of 111	
8	Micronucleus test in mice	DGD-1-11-A	22 of 22	4.2.3.3.2.1
9	Teratology study (rat)	DGD-1-8-A	11-13 of 249	
10	DRF Rat fertility/embryotoxicity	99-12-803	139-146 of 152	
11	Rat Fertility/embryotoxicity	99-12-804	333-343 of 354	4.2.3.5.2.1
12	DRF study in pregnant rabbit	99-12-801	108-111 of 119	
13	Embryotoxicity study in rabbit	99-12-802	244-250 of 263	
14	Acute SC Toxicity (rat)	DGD-1-14-A	22 of 78	
15	Acute IM Toxicity (rat)	DGD-1-15-A	7 & 22 of 78	4.2.3.6.1
16	Local Tolerance in rabbit	DGD-33-002	113-127 of 127	
17	Immunotoxicity study (Guinea-pig)	DGD-33-003	90-102 of 102	4.2.3.7.2.1
18	Impurities [REDACTED] (b) (4)	[REDACTED]	[REDACTED]	[REDACTED]

Source: Reviewer's table; DRF= Dose Range Finding

You should send your response to me electronically at James.Moore@fda.hhs.gov and provide a copy to Dr. Olayinka Dina at Olayinka.Dina@fda.hhs.gov. Follow up the requested electronic document with a submission to your NDA file. Please provide this information as soon as possible.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
11/07/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: November 7, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 4, NDA 204-781, Dotarem Injection, Diagnoses Tabulation	

Total no. of pages including cover: 2

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November 7, 2012

Regarding your pending NDA 204-781 for Dotarem, the clinical reviewer has the following comments and information requests.

1. Provide a breakdown of subject referral diagnoses by numbers and percent of subjects for both phase 3 pivotal trials. For study DGD-44-050 include primary brain tumors (benign and malignant), metastatic disease, inflammation, vascular processes, infection, and other such as multiple sclerosis.
2. Since the DGD-44-051 trial excluded subjects with a non tumoral diagnosis, provide a similar listing for the DGD-44-051 study based on tumor disease only.
3. For each study, note the number and percent of subjects referred for evaluation of the spinal cord.
4. For study DGD-44-051, provide the strength (magnetic field Tesla) of the equipment used for the study.

Provide an electronic copy to me at James.Moore@fda.hhs.gov and send a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov. Follow up this electronic submission to me with a submission of this document to your NDA file. You should provide this document electronically to me by COB Friday, November 9, 2012.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager

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/s/

JAMES W MOORE
11/07/2012



Food and Drug Administration
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 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: October 31, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet LLC	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request 3, NDA 204-781, Dotarem Injection, Study Sites, Core Labs	

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October 31, 2012

The review of your pending NDA 204-781 for Dotarem is ongoing. However, the clinical reviewer has several comments and information requests regarding your clinical studies.

1. We've received the information from Guerbet on the study sites and core lab. Are there additional sites that maintain study files? Are there any associated sites that might need inspection?
2. Guerbet listed three (b) (4) sites. Were all of these sites considered core labs and were these the sites for the blinded reading of the images from the Pivotal studies? Were the files from these reading/evaluations (b) (4)

Please respond to this request by COB, Friday, November 2, 2012.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
10/31/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: October 25, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Regulatory Request1, Telephone Conference, NDA 204-781, Dotarem, Filing Issues	

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October 25, 2012

Regarding your pending NDA for Dotarem, NDA 204-781, the Division requests a brief (< 30 min) telephone conversation to discuss the following items:

1. Potential NDA 204781 filing issues: we have identified the following items that must be resolved:
 - a. Navigational tools (hyperlinks) are lacking in both the documents and the Table of Contents
 - b. Incorrect data entries and documents placed in incorrect locations, for example for study DGD-44-050 protocol deviations listed are for an MRA study and for this same study, an efficacy listing is cited as an adverse event
 - c. Case report forms for safety (SAEs) appear to be in an incorrect location (per IT); there are no separate CRFs for deaths and there are no CRFs for withdrawals/discontinuations or for subjects with protocol deviations
 - d. Manufacturing facilities are not registered for inspections; we need the registration number to initiate the inspection; lack of this number means your facility is not ready for Inspection.

2. During our initial examination of your NDA, we could not locate the main data supporting the use of the drug in patients < 2 years of age. What data are intended to support this use? It appears that you report only 7 subjects (< 2 years of age) as having exposure to your drug in clinical studies and you supply no PK data in this population. Additionally, you appear to supply no preclinical data to support the safety of this use. We have been requesting sponsors to supply preclinical data and clinical imaging/PK data if they desire to seek the use of a GBCA in patients < 2 years of age. If you do not have/or can not identify the data supporting your proposal for use of your drug in patients < 2 years of age, you may wish to amend your proposed labeling (indication) to limit your drug's use to patients > 2 years of age. While we welcome data supporting the pediatric use (< 2 yrs), we anticipate the need for an advisory committee discussion if your drug is proposed for use in this population.”

The telephone conference has been tentatively scheduled for Wednesday, October 31, 2012 from 12:00PM-12:30PM EST. Please let me know if that date and time is acceptable and if it is please provide a call in number.

If you have questions, please contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
10/25/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: October 22, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request2, NDA 204-781, Dotarem, Study Summaries	

Total no. of pages including cover: 2

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Document to be mailed: YES x NO

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October 22, 2012

Regarding the study synopses for pending NDA 204-781 for Dotarem® (gadoterate meglumine) Injection, the clinical reviewer has the following comments and information requests.

The clinical summary section (module 2.7.6) contains study synopses with numerous publications and post marketing studies.

1. Please clarify which studies are numbered and which are not numbered and why.
2. Please state which studies and study phase you consider as supportive evidence of drug efficacy for the CNS indication.
3. Please state which of these studies were originally performed as confirmatory and which are post marketing studies.
4. In your response, please cite the page (#/135) referring to the study.

You should provide the information electronically to me at James.Moore@fda.hhs.gov and provide a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov. Follow up this submission with a submission to your pending NDA file. You should provide this information by COB Wednesday, October 24, 2012.

If you have questions, please contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
10/22/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: October 15, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Clinical Request1, NDA 204-781, Dotarem, Clinical Sites	

Total no. of pages including cover: 2

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October 15, 2012

Regarding your pending NDA for Dotarem, NDA 204-781, the clinical reviewer has the following information requests. Please provide the following:

1. The number of patients at each clinical trial site.
2. The number of Adverse Events at each site.
3. The number of Serious Adverse Events at each site.
4. The number of protocol violations at each site.
5. The number of patient withdrawals at each site.
6. Names and contact information for each investigator at each site.
7. The address and contact information for the Core Lab responsible for the blinded reading of images for your clinical trials.

Provide this information to me electronically at James.Moore@fda.hhs.gov and send a copy to Dr. Barbara Stinson at Barbara.Stinson@fda.hhs.gov by COB Tuesday, October 23, 2012. Follow up your electronic submission to me with a submission to you NDA file.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
10/15/2012



Food and Drug Administration
 Center for Drug Evaluation and Research
 Office of Drug Evaluation OODP

FACSIMILE TRANSMITTAL SHEET

DATE: October 5, 2012

To: Corina Harper, RAC, Compliance Manager	From: James Moore
Company: Guerbet	Division of Medical Imaging Products
Fax number: 812-333-0084	Fax number: (301) 796-9849
Phone number: 812-333-0059	Phone number: (301) 796-1986
Subject: Chemistry Request1, NDA 204-781, Dotarem, Samples	

Total no. of pages including cover: 2

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October 5, 2012

Regarding your pending NDA 204-781 for Dotarem® (gadoterate meglumine) injection, the chemistry reviewer has the following information request and comment.

1. Provide representative samples of the Dotarem product for each vial and pre-filled syringe presentation.

These representative samples will not be used for any clinical or product quality testing.

Please provide your response to this request by COB, Monday, October 15, 2012.

If you have questions, contact me at (301) 796-1986.

James Moore, PharmD., M.A.
Regulatory Health Project Manager, DMIP

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/s/

JAMES W MOORE
10/05/2012



NDA 204-781

NDA ACKNOWLEDGMENT

Guerbet LLC
Attention: Corina Harper, RAC
Head of North America Scientific Office
1185 West 2nd Street
Bloomington, IN 47403

Dear Ms. Harper:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Dotarem®(Gadoterate Meglumine) Injection

Date of Application: September 20, 2012

Date of Receipt: September 20, 2012

Our Reference Number: NDA 204-781

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 19, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1986.

Sincerely,

{See appended electronic signature page}

James Moore, PharmD., M.A.
Regulatory Health Project Manager
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

JAMES W MOORE
10/02/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 65,041

MEETING MINUTES

Guerbet LLC
Attention: Corina Harper, RAC
Head of North America Scientific Office
1185 West 2nd Street
Bloomington, IN 47403

Dear Ms. Harper:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Dotarem (gadoterate meglumine) Injection.

We also refer to the meeting between representatives of your firm and the FDA on June 12, 2012. The purpose of the meeting was to discuss the proposed submission of a New Drug Application (NDA) for Dotarem®(gadoterate meglumine) Injection.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call James Moore, Regulatory Health Project Manager at (301) 796-1986.

Sincerely,

{See appended electronic signature page}

Rafel D. Rieves, M.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Industry Meeting between the Division of Medical Imaging Products and Guerbet,
Building 22, Conference Room 1315, Tuesday, June 12, 2012, 12 PM-1PM, FDA White
Oak Campus, Silver Spring, Maryland

Subject: Dotarem (gadoterate meglumine), I 65,041, (Pre-NDA Meeting)

FDA Attendees:

Rafel D. Rieves, M.D., Director, DMIP
Liberio Marzella, M.D., Ph.D., Deputy Director, DMIP
Alexander Gorovets, M.D., Clinical Team Leader, DMIP
Barbara Stinson, D.O., Clinical Reviewer, DMIP
Yanli Ouyang, Ph.D., Pharmacology/Toxicology Reviewer, DMIP
Anthony Mucci, Ph.D., Statistical Reviewer, OB
Jyoti Zalkikar, Ph.D., Statistical Team Leader, OB
Eldon Leutzinger, Ph.D., Chemistry Reviewer, ONDQA
Kevin Wright, PharmD., Safety Evaluator, OSE
Sandra Griffith, R.N., Safety Project Manager, OSE

Guerbet Attendees:

Phillipe Bourrinet, PharmD., Head of Global Regulatory Affairs and Non-Clinical
Development
Pierre Desch', M.D., VP Medical and Regulatory Affairs
Jing Hao, M.D., Clinical Project Manager
Romuald Laine, Ph.D., Project Manager
Isabelle Raynal, Project Manager Associate
Choung-Ho Tuong, PharmD., Regulatory Affairs Pharmacist
Phillippe Zamia, Ph.D., Biostatistician
Kawathat Kehal, M.D., Medical Pharmacovigilance Advisor
Corina Harper, Head of North America Scientific Office
Alletah Schmidt, Regulatory Affairs Associate

Background

Prior to the meeting a response to questions from Guerbet's meeting package was sent to them. Here is the Division's meeting response. After introductions the meeting began with a presentation by Guerbet.

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B Meeting
Meeting Category: Pre-NDA
Meeting Date and Time: Tuesday, June 12, 2012
Meeting Location: Building 22, Conference Room 1315
Application Number: I 65,041
Product Name: Dotarem
Indication: CNS Imaging
Sponsor/Applicant Name: Guerbet

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 12, 2012, FDA White Oak Campus, Building 22, Conference Room 1315, Tuesday, June 12, 2012, 12 PM-1 PM between Guerbet and the Division of Medical Imaging Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

2. DISCUSSION

The questions and responses are organized by discipline. Your questions are *italicized* and FDA's responses are **bolded**.

Guerbet would appreciate receiving guidance on the following specific questions (grouped by discipline).

Nonclinical

Sponsor's Question 1:

Module 4 will contain both nonclinical studies performed for the initial registration of Dotarem in Europe as well as some toxicology studies that were requested by the FDA in May 1999 to be repeated at higher dose levels plus some additional toxicology and safety

pharmacology studies, requested by FDA in September 2000. A number of safety pharmacology studies were conducted prior to the implementation of ICH guideline S7A in 2000 and consequently were not performed in compliance with GLP. However, they were done according to the state of the art at the time of performance and Guerbet considers that repeating those studies just for GLP compliance purpose would not bring any additional scientific information and would be of ethical concern based on unnecessary use of additional test animals.

Upon request from the FDA, Guerbet submitted (April 22, 2010) an update of nonclinical studies performed, the study results, and GLP compliance status in the format of a draft nonclinical written summary (module 2.6). To date, no specific feedback has been received from the FDA regarding that submission, and particularly, no request for additional studies has been made. A tabular overview of nonclinical studies which will be included in the NDA is provided in this Briefing Document (Section 3).

Does the FDA agree that the proposed non-clinical pharmacology and toxicology data package is sufficient and adequate to support NDA submission?

FDA's Response to Question 1:

Yes. Your nonclinical data, as submitted in April, 2010 and provided as an overview in the Briefing Document, appears sufficient and adequate to support your proposed NDA submission.

Chemistry Manufacturing and Controls

Sponsor's Question 2:

Environmental Assessment (EA): Guerbet would like to apply for a categorical exclusion for EA in the NDA, for the reason described hereafter. The active moiety of gadoterate meglumine on MR signal is the paramagnetic gadolinium ion. This active moiety is also common to all other already US-approved and marketed Gd-based contrast agents (Magnevist, Omniscan, ProHance, Gadavist, Multihance, Optimark, etc). The proposed indication and posology for Dotarem is also approved for the agents mentioned above. Therefore, if the FDA approves Dotarem, this will not lead to an increase of environment exposure to the active moiety (Gd), as Dotarem will take market shares to already approved products in the same indication. The non-increase of use of the active moiety in the USA is a criterion for categorical exclusion for the need to provide an EA in the NDA.

Does FDA agree to grant a categorical exclusion to provide an EA in the NDA, on the basis of a non-increase of environment exposure to the active moiety Gadolinium?

FDA's Response to Question 2:

We recommend that you refer to the Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications. The rules under 25 CFR 25.31 describe the conditions under which a claim for categorical exclusion may be submitted. The guidance further clarifies the process and calculations performed for claiming exclusion. The guidance may be found at the following FDA/CDER web page:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070561.pdf>

Clinical

Sponsor's Question 3:

Guerbet plans on submitting an NDA in order to seek a CNS indication for use of Dotarem as a contrast agent indicated for Intravenous use with magnetic resonance imaging (MRI) in the brain (intracranial), spine and associated tissues in adults and pediatric patients (2 years of age and older) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

This submission will be based on two Phase 3 pivotal studies (a prospective study DGD-44-050 and a re-read protocol DGD-44-051 as agreed with the FDA on September 03, 2009) and 21 additional supporting studies in CNS indications.

Does the FDA agree that this efficacy data package appear to be sufficient to support NDA submission of Dotarem for the proposed indication?

FDA's Response to Question 3:

Yes. The efficacy data package appears sufficient to support NDA submission of Dotarem for the proposed indication. On review of the briefing document, we note that you have conducted 3 dedicated pediatric studies in patients less than 2 years of age for the CNS indication. Please explain why you are not seeking this additional age indication.

Sponsor's Question 4:

*The Integrated Summaries of Efficacy and Safety:
Efficacy:*

The primary focus of the Integrated Summary of Efficacy (ISE) will be on the comparison of the efficacy of Dotarem-enhanced MRI compared to unenhanced MRI in terms of lesion visualization. Confirmation of efficacy will be based primarily on the analysis in two pivotal Phase 3 studies. Supplemental efficacy analyses will be performed on data from 21 other clinical studies in the CNS indications. Efficacy results from the two pivotal studies will be individually analysed, and efficacy results from all other studies will be summarized in the ISE but no formal integration of efficacy will be performed.

Safety:

For the integrated summary of safety (ISS), all clinical Phase 1 to 4 studies for Dotarem (49 clinical studies for variable indications sponsored by Guerbet) will be pooled into one integrated analysis pool. Key analysis for safety will consist of:

- *Number and incidence of adverse events, drug-related adverse events, serious adverse events, and drug-related serious adverse events.*
- *Comparison of vital signs between pre and post injection.*
- *Comparison of laboratory parameters between pre and post injection.*
- *Analysis of subgroups, e.g. gender, age groups, race, risk population e.g. impaired renal function, liver function, allergy, important current diseases (cardiac diseases, diabetes, etc.).*
- *Summary of post marketing experience from March 31, 1989 (International Birth Date) to March 31, 2012 (Data Lock Point) including:*
 - *patient exposure,*
 - *a cumulative analysis using a Risk Management approach (identified risks/potential risks, including drug interactions), with cases presented according to the relevant Standardized MedDRA Queries (SMQs) as well as according to the System Organ Class (SOC) classification,*
 - *a cumulative analysis of misuse, off-label use, medications errors,*
 - *a specific section dedicated to deaths cases and their causes,*
 - *a specific section on nephrogenic systemic fibrosis (NSF).*

Does the agency agree with the proposed data pools and key analyses that will be included in the ISE and ISS?

FDA's Response to Question 4:

The proposed data pools and analyses are acceptable for the ISE. For the ISS analyses, we recommend analyses similar to those you have proposed for the CNS studies and for the pediatric population in addition to the pooled analyses for the 49 studies. For the ISS, please submit complete analyses, not just summaries.

Sponsor's Question 5:

Dotarem has been shown to have one of the lowest risks of NSF due to its ionic macrocyclic structure and consequently its high stability. In Europe, Dotarem has been classified in the "low risk" category for NSF risk, and maintained as such upon the assessment of the last annual cumulative safety review which was submitted to the European authorities (July 26, 2011) and will be submitted in the NDA. Considering that the labelling proposed for Dotarem will be sufficient to address the risks associated with the product, including the risk of NSF, and that there is no need for any other risk minimization action, Guerbet does not intend to submit a REMS.

Does the FDA agree that there is no need for Guerbet to submit REMS?

FDA's Response to Question 5:

We agree that no REMS is anticipated, based upon our current understanding of the proposed claims and supportive data. Please note that additional information regarding risks and product safety could emerge during the review of your NDA. Therefore, a full clinical review after the NDA is submitted will be necessary to definitively determine whether a REMS is necessary to ensure the benefits outweigh the risks.

Sponsor's Question 6:

Regarding post-marketing experience reports, Guerbet proposes to provide in Module 5 the following successive Periodic Safety Update Reports (PSURs) which have been submitted to European authorities, and to summarize each of them individually in Module 2.7:

- *5-years Periodic Safety Update Report from 04/01/1994 to 03/31/1999*
- *1-year Periodic Safety Update Report from 04/01/1999 to 03/31/2000*
- *1-year Periodic Safety Update Report from 04/01/2000 to 03/31/2001*
- *1-year Periodic Safety Update Report from 04/01/2001 to 03/31/2002*
- *Line listing covering the period from 04/01/2002 to 09/30/2002*
- *5-years Periodic Safety Update Report from 10/01/2002 to 09/30/2007*

- *3-years Periodic Safety Update Report from 10/01/2007 to 09/30/2011*
- *6-month Periodic Safety Update Report from 10/01/2011 to 03/31/2012*
- *Cumulative summary tabulation of serious events from 04/01/1994 to 03/31/2012*

Does the FDA agree with this proposal?

FDA's Response to Question 6:

This approach is acceptable. However since your anticipated date of submission is in September, the safety data for the submission should be extended to cover the time frame up to about 3 months prior to the submission. In addition, please be advised that a 120 day safety update will be required once the review is ongoing.

Statistical and Electronic Datasets

Sponsor's Question 7:

There are a large number of individual clinical study reports that will be included in the submission reflecting the comprehensive development program conducted to date in Phase 1-4. We will submit Guerbet analysis datasets (in Microsoft® Excel format) to accompany each of the studies listed. The Guerbet analysis datasets contain all raw data as collected from the clinical trial CRFs as well as additional derived variables and derived datasets created specifically to support study analyses. All statistical programs written in SAS for statistical table generation utilized Guerbet analysis datasets as input. In addition, datasets for integrated efficacy and safety analyses will be provided in SAS version transport file format.

Does the agency agree with the proposed format of the electronic datasets to be submitted?

FDA's Response to Question 7:

Yes. Note that, on the basis of preliminary perusals of the submitted data sets, it is possible that the Statistical Reviewer might request additional derived data sets and additional tables to facilitate the review.

Regulatory

Sponsor's Question 8:

Does the FDA agree that the proposed Table of Contents for the NDA (Appendix 1) indicates appropriate content to support submission?

FDA Response to Question 8:

The TOC for clinical appears acceptable. Other sections of the TOC also appear acceptable.

The NDA should include a Summary of Clinical Pharmacology Studies (eCTD section 2.7.2). The analytical methods for each of the clinical pharmacology studies should be summarized, and raw validation and analytical run data provided, in Summary of Biopharmaceutic Studies and Associated Analytical Methods (eCTD section 2.7.1). All the raw pharmacokinetic (PK) data (concentration-time data together with study/patient ID, dose, and demographic data) for all patients contributing PK data to the NDA should be submitted electronically as a single .xpt file.

As an aid to our review of your QT assessment we request that you

- 1) include an estimate of the power of your approach, i.e., an estimate of the minimal change in QT/QT_C that can be “ruled out” using a confidence interval approach under the assumption that Dotarem has minimal or no effect on QT/QT_C , and
- 2) complete the attached “Highlights of Clinical Pharmacology” table. We understand that information for selected items may be inapplicable to your intravenously administered drug product.

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC

Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered	

Scenario	by the supra-therapeutic dose.
----------	--------------------------------

Sponsor's Question 9:

A common Package Insert will be proposed for both commercial presentations; single dose presentation in vials or pre-filled syringes (PFS) and pharmacy bulk package in vials.

Does the FDA agree this approach is acceptable?

FDA's Response to Question 9:

This is acceptable.

Sponsor's Question 10:

Does FDA believe that Guerbet will be asked to present the dossier and data included to the review Division shortly after NDA submission (Applicant orientation meeting)?

If yes, could FDA provide guidance on expected timeframe and content of this kind of meeting?

FDA's Response to Question 10:

We anticipate an applicant orientation meeting will be held within 45 days of submission.

Sponsor's Question 11:

Does the FDA believe that an Advisory Committee will be required during the review process of the NDA?

FDA's Response to Question 11:

It is premature to definitively comment on whether an Advisory Committee meeting will be held for Dotarem since a preliminary examination of your application is necessary and important considerations in the GBCA field may evolve between now and your NDA submission. If an Advisory Committee is anticipated, we will inform you as soon as feasible following our initial examination of your NDA.

Sponsor's Question 12:

Does the FDA have any other advice to provide Guerbet for the proposed NDA?

FDA's Response to Question 12:

We have the following additional comments:

- 1. We note that most of the readers' mean scores for the DGD-44-050 SPA study were considerably higher (often double) than those for the re-read. What do you attribute this difference to? Please comment.**
- 2. Please confirm that all original source material for the re-read protocol is available.**
- 3. As you may know, PDUFA V expectations may impact your NDA if it is submitted after October 1, 2012. Information regarding the anticipated expectations for NDAs submitted after this date is available on the FDA website at: <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>**

Discussion

Guerbet did not ask for additional clarification of questions 1, 2, 5, 8, 9, 10, 11, 12-3 and those questions were not discussed. Questions 3, 4, 6, 7 and question 12, parts 1-2 were discussed.

Question 3

Most of the discussion under question 3 focused on the data available on the use of Dotarem in the pediatric population. This discussion was prompted by FDA's response in which the Division asked why Guerbet was not pursuing a pediatric indication for patients 0-2 years of age.

Guerbet responded with the following information at the meeting: (1) There were no pivotal studies conducted in this age group (2) because of the occurrence of nephrogenic systemic fibrosis in patients with reduced renal function a proposed indication in a population with immature renal function could be considered provocative and (3) the studies done for the CNS indication only targeted adults.

FDA inquired of Guerbet the number of pediatric patients less than 1 month of age that were included in their efficacy trials. Guerbet stated that they were unsure of the number but would provide that in a subsequent submission.

FDA inquired if Guerbet had performed studies in juvenile animals that could support the safety of Dotarem in pediatric patients. Guerbet replied that they had not.

Guerbet described the distribution of pediatric data within the Dotarem development program. Guerbet stated that they will provide a complete listing of the pediatric patients they have studied in their NDA and it will be displayed by age group from 0-17 years.

FDA inquired of Guerbet whether the source data was available for the studies in the pediatric patients. Guerbet replied that it was.

Guerbet said that there have not been any confirmed cases of nephrogenic systemic fibrosis using Dotarem in either the pediatric or the adult population. Guerbet further stated that cases of Nephrogenic Systemic Fibrosis (NSF) noted with the use of Dotarem have all been confounded cases.

According to Guerbet there have been three cases of NSF in which other agents including Dotarem were used. According to Guerbet there was an initial case of NSF reported in Japan, but after histology it was proven not to be NSF.

Question 4

Guerbet requested clarification of the response provided by FDA to this question because the response appeared redundant. FDA clarified that the response should have stated that the analyses were for the ISS not the ISE as noted in the meeting response.

Guerbet stated, for the ISE they plan to submit data from two pivotal Phase 3 studies, and 21 supportive studies for a total of 23 studies for the CNS indication.

FDA encouraged Guerbet to provide a safety database that included pediatric patients only. Guerbet responded that they would. FDA asked Guerbet to stratify the database by age group, 0-2, 2-5, 5-11 and 12-17.

Guerbet stated that they have a total of 23 efficacy studies devoted to the CNS indication and a total of 49 studies for various indications that will constitute the safety database.

Question 6

Guerbet sought agreement from FDA to submit their Safety Update (SU) at a time point other than the one requested by FDA in the Division's response. Guerbet asked that they be permitted to provide safety data in their NDA that had a data lock date of March 31, 2012 (6 months prior to NDA submission, FDA requested 3 months) presuming that the NDA is submitted in September, 2012. Guerbet stated they will (presuming that the NDA is submitted in September, 2012) provide a SU four months into the NDA review cycle (January, 2013). FDA acknowledged this proposal as reasonable.

Question 7

Guerbet asked FDA to clarify their response to question 7 from the meeting package that referenced datasets. FDA responded that in the course of the review of the statistical datasets there may be a need to request additional analyses, further stratification of the datasets or additional data in support of the review of the application.

Question 12, Part 1

Guerbet sought to clarify for FDA why there was a difference in scoring for blinded readers between studies. Guerbet stated that there is really no difference in reader scores between studies. The scores noted in the meeting package were a function of the study reviewed and the number of lesions seen by the readers. According to Guerbet the difference in mean scores can be explained by the patient population. For example in study 50 patients presented with an average of 2-3 lesions and in Study 51 patients presented with an average of 1 lesion.

Question 12, Part 2

Guerbet noted that all original source material for the reread protocol is available to FDA.

Summary

Guerbet plans to submit an NDA for Dotarem in September, 2012. The proposed indication will be "Dotarem (gadoterate meglumine) Injection is indicated as a contrast agent for intravenous use with magnetic resonance imaging (MRI) in the brain (intracranial), spine and associated tissues in adults and pediatric patients (neonates to 17 years) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity." The pediatric safety data will be stratified by age group (0-2yrs, 2yrs-5yrs, 5yrs-12yrs, 12yrs-17 yrs). All source data for the reread will be available to FDA. Guerbet will submit 2 pivotal Phase 3 studies and 23 supportive studies in support of the efficacy of Dotarem. Data from forty nine studies will be submitted in support of the safety of the product.

The minutes were prepared by James Moore, Regulatory Health Project Manager.

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[Office of Drug Evaluation IV]
[DMIP]

Meeting Minutes
[Type B-Pre NDA]

Slides

11 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES W MOORE
07/11/2012

RAFEL D RIEVES
07/12/2012